Regulation of Vascular Tone

The Fat Connection

Maria S. Fernández-Alfonso

The study of vascular tone regulation has been based traditionally on layer-specific mechanisms. Three different layers form the blood vessel wall: intima, media, and adventitia. The intima is a monolayer of endothelial cells, which separates circulating blood from the medial layer underneath. The media consists of concentric layers of smooth muscle cells and elastic lamella, varying in number depending on the vessel size. The outer layer of the vessel, the tunica adventitia, is formed of collagen bundles, elastic fibers, fibroblasts, and vasa vasorum. It also harbors perivascular nerve endings.

The course of vascular function research has changed through the years. Most early functional studies characterized vasoconstrictor and vasodilator agents and their receptor types and subtypes. At the same time, a bulk of investigation focused on the neural regulation of medial function, characterized perivascular innervation in the adventitia and adventitial-medial border, and described both vasoconstrictor and vasodilator neurotransmitters. The identification in the 1980s of nitric oxide as an endothelium-derived relaxing factor reoriented vascular function studies of the next 2 decades. As a consequence, the endothelial layer is now considered as a paracrine tissue, which produces and releases a variety of contractile and relaxant factors that modulate medial function directly and indirectly through modulation of neurotransmitter release. During this time, the adventitia was regarded as a structural support for the media and its functional role was ignored. However, in recent years there is increasing evidence of a direct modulation of this layer on blood vessel function in a variety of situations. The development of an easy method to remove the adventitia will enable determination of the functional contribution of this layer in the near future and help to define the complex interactions and feedbacks between vascular layers.

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On top of these regulatory mechanisms, the precise understanding of vascular function requires the characterization and definition of the interactions between the blood vessel and its environment. In this regard, it has to be kept in mind that many blood vessels are surrounded by adipose tissue in variable amounts. In 1991, Soltis and Cassis demonstrated that perivascular fat reduced vascular contractions to noradrenaline in rat aorta. The originality of this work was to analyze the role of a tissue that was considered a passive structural support for the artery and that is, still, routinely removed for isolated blood vessel studies. This finding was reexamined by Löhni et al, who confirmed the inhibitory action of perivascular fat on aortic contractions to a variety of vasoconstrictors. This anticontractile action is induced by a transferable protein factor released by adipocytes, which the authors called adipocyte-derived relaxing factor (ADRF), in analogy to endothelium-derived relaxing factor. The inhibitory action of ADRF is mediated by tyrosine kinase pathways and opening of ATP-dependent K⁺ (K<sub>ATP</sub>) channels. In a second work, the same group characterized that the mechanism of ADRF release from rat aortic periadventitial tissue was dependent on calcium and cAMP.

In this context, this issue of Hypertension features an interesting study, which provides new insights and perspective into the role of periadventitial fat in the regulation of vascular tone. Verloren et al describe that perivascular fat has a vasodilatory effect on Sprague-Dawley rat mesenteric arteries, which involves the activation of vascular smooth muscle voltage-dependent K⁺ channels (K<sub>V</sub>). Interestingly, the channels activated by fat in mesenteric arteries (K<sub>V</sub>) differ from the channels proposed to be activated in the aorta (K<sub>ATP</sub>), suggesting that there are vascular regional differences in the effects of perivascular adipose tissue or, as the authors suggest, the existence of different ADRFs. A second relevant experimental observation is that the anticontractile effect of ADRF positively correlates with the amount of perivascular fat. As shown in this work, the resting membrane potential of mesenteric vascular smooth muscle cells is more hyperpolarized in intact mesenteric rings surrounded by fat than in rings without fat. These results strongly suggest that perivascular adipose tissue contributes to the maintenance of basal mesenteric artery tone. Whether similar results can be observed in other strains or species remains to be determined.

During the last decade, an important number of adipocyte-derived peptides have been identified. These factors are secreted into the plasma and play an important endocrine, as well as an autocrine, role in the regulation of white adipose tissue. The work of Verloren et al supports the hypothesis of a paracrine role of white adipose tissue in the regulation of vascular function. In addition to ADRF, there are other adipose tissue–derived candidates that might modulate vascular function, such as leptin or the adipose-tissue renin-angiotensin system (RAS). Leptin is an adipocyte-derived
hormone, with effects on blood pressure that are the result of 2 opposite actions, the release of nitric oxide and sympathetic excitation. Pharmacological experiments have demonstrated that leptin induces a direct vasodilatation on aorta and mesenteric arteries by the stimulation of nitric oxide and endothelium-derived hyperpolarizing factor release, respectively. In addition, leptin induces an indirect contractile effect through central stimulation of sympathetic nervous activity. Moreover, a complete RAS has been identified in adipose tissue. Until now, most of the studies regarding this system have been directed to adipose tissue physiology, more than to a possible paracrine role of this local system on vascular function. This issue would be of special interest, because the inhibitory effect of both ADRF and leptin on angiotensin II–induced contractions is more potent than their anticontractile effect on other vasoconstrictors. This suggests that a balance between adipose tissue–derived vasodilator and vasoconstrictor factors might be essential for the maintenance of vascular resistance.

**Future Directions**

An essential question that remains to be answered concerns the chemical structure of ADRF. The identity of ADRF with leptin has been discarded, because the lack of functional leptin receptors in the Zucker fa/ fa rats did not modify the effect of perivascular fat. However, the fact that both ADRF and leptin induce hyperpolarization in mesenteric arteries should be taken into account, and the identity of ADRF with leptin or a leptin fragment should be considered in future studies.

On the other hand, the role of periadventitial fat on vascular function in a number of pathophysiological situations, particularly in obesity and metabolic syndrome, needs to be analyzed. In light of the present study, there seems to be a contradiction between the inhibitory effect of perivascular adipose tissue depending on the amount of fat, and obesity-related hypertension. One hypothesis that needs to be assessed is if obese models or patients are resistant to the vascular anticontractile effect of adipose tissue–derived factors, as they are to the metabolic effects of insulin or leptin. Another question that remains to be answered, is if there is a shift in the balance between adipose tissue–derived vasodilator and vasoconstrictor factors in obesity. The potential involvement of perivascular fat and adipose tissue–derived factors in the paracrine regulation of vascular tone will be a fascinating topic in the next years.

**References**

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